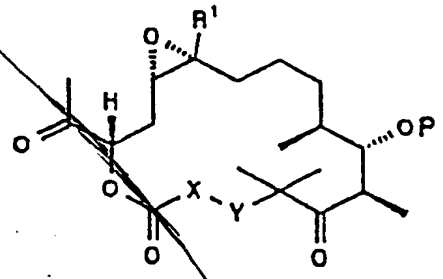
International Patent Application PCT/EP 99/03 159
based on DE 198 20 599.6
Hoefle et al.; Epothilone derivatives etc.

Patent Claims

1. Epothilone derivative of formula (2)



wherein R^1 is a hydrogen atom or a C_{1-8}-alkyl group, X-Y is a group of formula $-CH_2CH-OP$ or $-CH=CH-$, and
P is a protective group, wherein
X-Y is excluded as group of formula $-CH_2CH-OP$ if R^1 means a hydrogen atom or a C_{1-4}-alkyl group.

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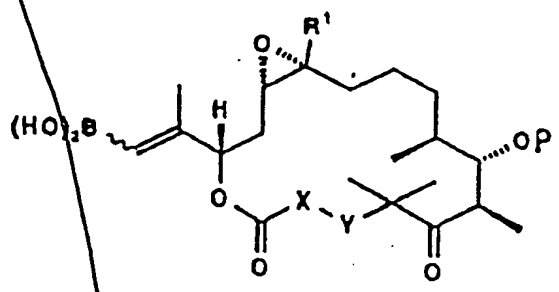
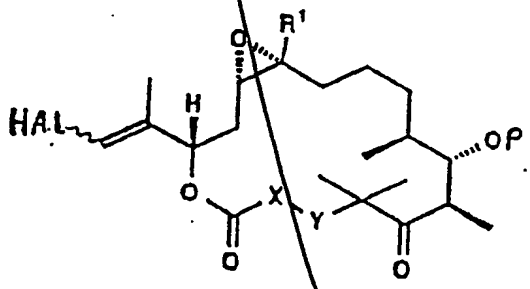
2. Epothilone derivative of formula (3)



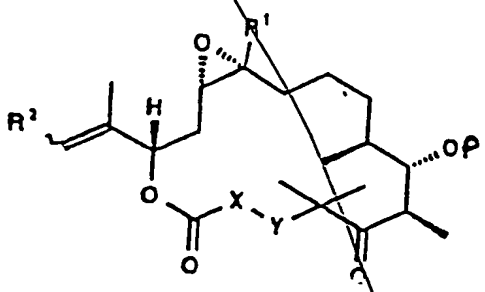
wherein the residues are as defined in claim 1.

3. Epothilone derivative of formula (4)



wherein the residues R^1, X-Y and P are defined as in claim 1, and Hal is a halogen atom such as Br or I.

4. Epothilone derivative of formula (5)



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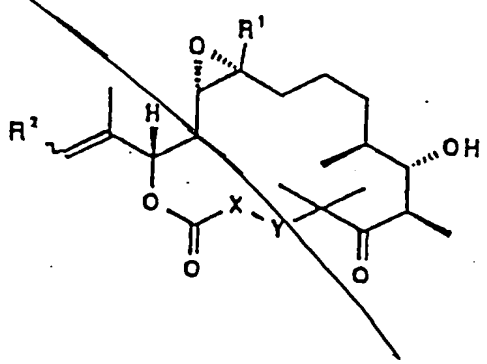
wherein the residues R^1, X-Y and P are defined as in claim 1, and R^2 is a monocyclic aromatic which can be substituted by a halogen atoms and/or OR^4- and/or NR^5R^6- and/or alkyl, alkenyl and/or alkinyl groups in ortho- and/or meta- and/or para-position, or a monocyclic 5- or 6-membered hetero aromatic, which can be provided with one or several O- and/or N- and/or S-atoms in the ring and/or which can be provided with OR^4- and/or NR^5R^6- and/or alkyl, alkenyl and/or alkinyl groups as substituents, wherein the residues R^4, R^5 and R^6 independently are defined as R^1 in claim 1, but are independent of R^1, wherein

(i) XY is excluded as group of formula -CH=CH- if R^1 is a hydrogen atom or a C_{1-4}-alkyl group and R^2 is a monocyclic hetero aromatic having a N atom and a S atom in its ring and a C_1-alkyl substituent and

(ii) X-Y is excluded as group of formula $-CH_2-CH-OP$ if R^1 is a hydrogen atom or a C_{1-4}-alkyl group and R^2 is a monocyclic hetero aromatic having a N atom and a S atom in its ring and a C_1-alkyl substituent.

5. Epothilone derivative of formula (6)



wherein the residues are defined as in claim 4 and, if X-Y means a group of formula $-CH_2CH-OP$, the protective group P has been removed, wherein

(i) XY is excluded as group of formula -CH=CH- if R^1 is a hydrogen atom or a C_{1-4}-alkyl group and R^2 is a monocyclic hetero aromatic having a N atom and a S atom in its ring and a C_1-alkyl substituent and

(ii) X-Y is excluded as group of formula $-CH_2-CH-OP$ if R^1 is a hydrogen atom or a C_{1-4}-alkyl group and R^2 is a monocyclic hetero aromatic having a N atom and a S atom in its ring and a C_1-alkyl substituent.

6. Epothilone derivative according to ~~any of the preceding claims,~~ **characterized** in that R^1, R^4, R^5 and R^6 are a hydrogen atom or a C_{1-6}-alkyl group, especially a C_{1-6}-alkyl group.

7. Epothilone derivative according to ~~any of claims 4 to 6,~~ **characterized** in that the substituents of the monocyclic aromatic and/or hetero aromatic are C_{1-6}-alkyl, C_{2-6}-alkenyl and C_{2-6}-alkinyl groups, respectively, especially C_{1-4}-alkyl, C_{2-4}-alkenyl and C_{2-4}-akinyl groups, respectively and the halogen atoms fluoro, chloro, bromo or iodo atoms.

8. Epothilone derivatives according to ~~any of claims 4 to 7,~~ **characterized** in that the aromatic and hetero aromatic, respectively, is provided with 1, 2 or 3 substituents and the hetero aromatic is provided with 1, 2 or more and especially 1, 2, 3, or 4 hetero atoms.

9. Process for the production of a compound of formula (3),

characterized in that a compound of formula (2) is reacted with the compound of formula $HC[B(OR)_2]_3$ if wanted in the presence of a base, wherein the residues are defined as in ~~any of the preceding claims~~ Claim 1 and R is defined as R^1, but is independent of R^1.

10. Process for the production of a compound of formula (4), characterized in that a compound of formula (3) is reacted with N-iodo- or N-bromo succinimide and that the residues are defined as in ~~any of the preceding claims.~~ Claim 1

11. Process for the production of a compound of formula (5), characterized in that a compound of formula (3) is reacted by a Suzuki coupling with a compound of formula R^2-Z , wherein R^2 is defined as in ~~any of the preceding claims~~ Claim 1 and Z can be a halogen atom or a group of formula $-OSO_2CF_3$, $-CH=CHI$, $-CH=CHOSO_2CF_3$.

12. Process for the production of a compound of formula (5), characterized in that a compound of formula (4) is reacted by a silent coupling (stille Kupplung) with R^2-SNR^3_3, wherein R^2 is defined as in ~~any of the preceding claims~~ Claim 1 and R^3 is a C_{1-6}-alkyl group, especially a C_{1-4}-alkyl group, preferably a methyl, ethyl, propyl or butyl group.

13. Process for the production of a compound of formula (6), characterized in that the protective group is removed from a compound of formula (5).

14. Process for the production of a compound of formula (6), characterized in that it comprises the process steps as disclosed in claims 9, 10, 11 or 12 and 13, wherein the residues are defined as in the preceding claims.

15. Therapeutical agent, containing at least one of the compounds described in ~~claims 1 to 8~~ claim 1 and optionally usual carriers, diluents and/or auxiliary agents.

16. Therapeutical agent according to claim 15, **characterized** in that it is a cytostaticum.

17. Plant protecting agent in agriculture and/or forest culture and/or horticulture, containing at least one compound described in ~~claims 1 to 8~~ claim 1 and optionally usual carriers, diluents and/or auxiliary agents.

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